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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/465,322	06/05/95	SODERLUND	H	A129S PCT/US

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JEFFREY I. AUERBACH, ESQ
HOWREY & SIMON (BOX NO. 34)
1299 PENNSYLVANIA AVE. N.W.
WASHINGTON, DC 20004-2402

EXAMINER	
MYERS, C	
ART UNIT	**PAPER NUMBER**
1634	22

DATE MAILED: 05/28/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/465,322	Appl[illegible]s) Soderlund
	Examiner Carla Myers	Group Art Unit 1634

☒ Responsive to communication(s) filed on *Dec 3, 1998* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *51-69* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *51-69* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the amendment of Paper No. 21, filed 12/3/98. Applicants arguments presented in the response of Paper No. 21 have been fully considered but are not persuasive to overcome all grounds of rejection. This action is made final.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not appear to provide support for the embodiment of "reagents" which comprise a target nucleic acid, a primer and a double stranded hybrid. Firstly, the specification does not describe any methods in which a double-stranded hybrid is formed. While the method described in the specification results in the formation of products which have a double-stranded region and a single-stranded region, the specification does not specifically teach primers which hybridize to the all but one nucleotide of the target and when extended by polymerase form a fully double-stranded molecule. Secondly, the specification as originally filed does not provide support for the concept of a composition or kit in which both the unreacted reagents (primer and target nucleic acid) are present with the final reaction products ("double-stranded hybrid").

4. Claims 51-69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51-68 are indefinite over the recitation of "A reagent" because "A reagent" refers to a single product and not to multiple products. It is unclear as to what Applicants are intending to claim by "A reagent". For example, it is unclear as to whether Applicants intend to claim a composition of reagents or kit comprising reagents. Clarification of the claims is required.

Claim 68 is indefinite over the recitation of "double stranded hybrid" because it is unclear as to what constitutes such a hybrid. For example, it is unclear as to whether this refers to a nucleic acid molecule that contains a double-stranded region and a single-stranded region or if this refers to a fully double-stranded molecule consisting of a target nucleic acid and a primer that has been extended.

Claim 69 is indefinite and confusing because it is not clear as to what constitutes "the sequence" in the phrase "wherein the sequence between the 3' end of the oligonucleotide detection primer and the specific nucleotide at the predetermined position in the target nucleic acid". Does this refer to the sequence on the strand that is being extended or the sequence of the target nucleic acid? In the later case, it is unclear as to how this sequence does not contain the same specific nucleotide as the predetermined position since the only sequence present between the primer and the predetermined sequence is the same nucleotide at the predetermined position. In the former case, it is unclear as to how this recitation further limits the claim or applies to the claim because the nucleotide immediately 3' to the primer would be

complementary to the nucleotide at the predetermined position and therefore couldn't possibly "contain a nucleotide residue of the same type as the specific nucleotide at the predetermined position". The claim as written implies that there are multiple nucleotides present between the 3' end of the primer and the predetermined position. However, the claim also indicates that no residues are present between the position complementary to the 3' end of the primer and the predetermined position since the primer flanks the 3' end of a predetermined position. Clarification of the claim is required. It is also unclear as to what is intended to be meant by "said detection primer extended by..." since the claim is drawn to a product and not to a process. In one aspect, the claim refers to a primer which flanks a predetermined position. Yet, the claim also refers to a primer that is extended to incorporate a nucleotide complementary to the predetermined position. Therefore, it is unclear as to what constitutes the oligonucleotide primer extension product.

5. Claim 69 is rejected under 35 U.S.C. 102(e) as being anticipated by Erlich.

Erlich (see, for example, col. 8) teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. In particular, Erlich teaches the primer "DB01" (see columns 29 and 30), which hybridizes to the target nucleic acid so that the 3' nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second nucleotide residue. It is pointed out that the 3' residue of the DB01 primer flanks the "CTT" codon, which is present as a "GTG" codon in

allelic variants and thereby the "C" nucleotide adjacent to the primer is considered to be a variable or mutated nucleotide and the "C" and "G" nucleotides are considered to be a first and a second "nucleic acid residue at a defined site". Hybridization of the primer to the target nucleic acid results in a primer extension product comprising an oligonucleotide primer hybridized to a target nucleic acid wherein the primer may be extended by a polymerase to add a nucleotide complementary to a predetermined position in the target nucleic acid.

6. Claims 51-53, 63-68 are rejected under 35 U.S.C. § 103 as being unpatentable over Erlich (U.S. Patent No. 5,310,893) in view of Mullis (U.S. Patent No. 4,683,202; cited in the IDS of Paper No. 5).

Erlich (see, for example, col. 8) teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. In particular, Erlich teaches primer "DB01" (see columns 29 and 30), which hybridizes to the target nucleic acid so that the 3' nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second nucleotide residue. It is pointed out that the 3' residue of the DB01 primer flanks the "CTT" codon, which is present as a "GTG" codon in allelic variants and thereby the "C" nucleotide adjacent to the primer is considered to be a variable or mutated nucleotide and the "C" and "G" nucleotides are considered to be a first and a second "nucleic acid residue at a defined site". Erlich teaches that primers may be 15 to 25 nucleotides in length (col. 4) and teaches that the DB01 primer is 21 nucleotides in length (col. 29). Erlich also teaches that, following the amplification reaction, the sequence of sample nucleic acids can be

determined and confirmed by dideoxy chain termination sequencing. It is conventional in the field of dideoxy chain termination sequencing to use labeled dideoxyribonucleotide triphosphates to facilitate detection of the sequencing products. Erlich further teaches that the amplification reaction is performed using dNTPS and a polymerase. It is stated that the amplification may be performed using labeled reagents in order to allow for the detection of the amplification products and Erlich exemplifies methods in which the primers are labeled with detectable moieties (see, for example, col. 5). Erlich does not exemplify methods using labeled dNTPS. However, Mullis (col. 14) teaches that in PCR either the primer or the dNTPS may contain detectable moieties. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Erlich so as to have amplified the target nucleic acids using labeled dNTPs in place of labeled primers in order to have provided an equally effective means for facilitating detection of the amplification products. Such a modification of the method of Erlich would have resulted in a method which comprised the use of the reagents of a target nucleic acid, a DB01 oligonucleotide primer consisting of a sequence that hybridizes to the target nucleic acid immediately adjacent to a variable nucleotide position, labeled nucleotides and/or labeled dideoxynucleotide triphosphates, and a polymerase. Erlich does not specifically disclose a kit comprising each of these reagents. However, Erlich (col 26) does suggest that kits should be prepared containing all of the reagents required to practice the disclosed amplification technique wherein such kits comprise, for example, a primer, the substrate nucleoside triphosphates, means used to label, and an agent

used to catalyze primer extension. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated a kit for practicing the method of Erlich which contained the reagents of target nucleic acid, the DB01 amplification primer, labeled nucleotides or labeled dideoxynucleotides and a polymerase in order to have achieved the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claims 63 and 67, Erlich does not specifically exemplify a DB01 primer having attached thereto an "attachment moiety" through which the primer can be immobilized or immobilization of the primer and the amplification product onto a solid support. However, Erlich does teach that primers useful for amplifying variable nucleotides can be modified so as to attach labels thereto, including labels which can be used to capture the primer and facilitate immobilization of the primer onto a solid support (see col. 5). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the amplification primer of Erlich so as to have attached a moiety allowing for the immobilization of the primer in order to have accomplished the expected advantage of generating a primer which could easily immobilized onto a solid support to have allowed for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from other nucleic acids.

In the response of Paper No. 21, Applicants traversed the previous grounds of rejection by stating that the cited references do not teach the inclusion of a specific labeled nucleotide complementary to the predetermined position of the target nucleic acid. However, the combined references do teach the inclusion of labeled dNTPs which

comprise a specific labeled nucleotide complementary to the nucleotide immediately adjacent to the 3' end of the DB01 primer and thereby complementary to the variable/"predetermined" position of the target nucleic acid.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

May 25, 1999

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER